It's Not Necessarily All about the Delivery in Huntington's Disease

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Existing models of Huntington's disease posit that deficits in BDNF delivery to the striatum contribute to atrophy and motor impairment. In this issue of *Neuron*, Plotkin et al. (2014) show that BDNF delivery is normal but downstream signaling via TrkB and p75 is impaired, leading to corticostriatal synaptic dysfunction.

Huntington's disease (HD) is a fatal neurodegenerative disorder caused by a CAG repeat expansion in the gene encoding the huntingtin protein. This mutation results in progressive neurodegeneration that is most striking in the striatum. HD is characterized by motor incoordination and involuntary choreic or dance-like movements; the latter arise primarily as a result of the inability of aberrant cortical-striatal circuits to suppress unwanted motor output. Notably, prior to extensive cell death, subtle physiological changes are known to occur within the striatum (Raymond et al., 2011). Thus, there is hope for delaying or preventing the symptoms of HD by elucidating these early alterations and their underlying mechanisms. As the genetic cause of HD is known (The Huntington's Disease Collaborative Research Group, 1993), a variety of mouse lines have been generated that model the genetics, neuropathology, and motor impairments seen in human HD, and these models have proven invaluable to the understanding of this disease (Pouladi et al., 2013).

One of the early impairments is thought to be a reduction in the amount of brain-derived neurotrophic factor (BDNF) that is delivered to the striatum. The striatum itself expresses little to no BDNF and rather relies on anterograde transport and release of BDNF from cortical afferents for trophic support (Altar et al., 1997). As a result of the HD mutation, it has been shown previously that BDNF production in the cortex is reduced, as is its delivery to the striatum (Gauthier et al., 2004; Zuccato et al., 2001), and this is often cited as a plausible reason for the striatum's vulnerability in HD. In this issue of *Neuron*, Plotkin et al. (2014) use multiple primers and reference genes to convincingly show that BDNF production and delivery to the striatum in HD may not be as impaired as previously thought. They show, in both bacterial artificial chromosome (BAC) and heterozygous knockin (zQ175) mouse models of HD, that BDNF production by the cortex is normal, as is the activity-dependent activation of TrkB receptors in the striatum. Although the precise reasons for the inconsistencies among different studies and HD models remain unclear, Plotkin et al. (2014) suggest that the discrepancy is due in large part to the fact that previous studies compared BDNF expression to single reference genes that showed variable expression. It should be noted that Plotkin et al. (2014) observed some evidence of decreased cortical BDNF expression when they examined a more rapidly progressing homozygous knockin model of HD, and there is also evidence of reduced BDNF in postmortem tissue from human HD patients (Zuccato et al., 2008). Thus, although reduced BDNF expression and/or delivery to the striatum may contribute to HD pathology, the data presented in Plotkin et al. (2014) now, for the first time, question whether this deficit is a major pathogenic mechanism.

The BAC and heterozygous knockin HD models used in this study both exhibit progressive motor and cognitive symptoms, as well as HD-relevant neuropathology (Gray et al., 2008; Menalled et al., 2012). So, what role, if any, does BDNF play in these particular HD models? Instead of a delivery problem, the current study indicates that it is the processing of the BDNF signal in the striatum that appears to be aberrant in HD. The majority of the striatum is comprised of medium-sized spiny projection neurons (SPNs), which make up the well-established direct (dSPNs) and indirect (iSPNs) pathways of the basal ganglia responsible for movement initiation and suppression, respectively (Gerfen and Surmeier, 2011). In HD, the D2 dopamine receptor-expressing iSPNs are known to degenerate first, giving rise to involuntary, choreic movements. Later in disease progression, the D1 receptor-expressing dSPNs are affected, resulting in a shift toward an akinetic and rigid stage. Here, Plotkin et al. (2014) use a cleverly designed set of experiments to assess BDNF signaling in individual SPNs. They describe a form of synaptic plasticity that can be induced in single, phenotypically defined striatal neurons, is detected at the level of dendritic spines, and relies upon BDNF actions on postsynaptic TrkB receptors. As BDNF is delivered to the striatum via cortical and not thalamic afferents, they use channelrhodopsin to show that this form of plasticity is restricted to corticostriatal synapses. Strikingly, BDNF-dependent potentiation is progressively impaired in the HD striatum but only at cortical synapses onto iSPNs and not dSPNs, thereby providing a putative mechanism underlying the motor phenotype that plagues early symptomatic HD. The plasticity deficit is due to enhanced signaling downstream of the p75 neurotrophin receptor, which, along with the TrkB receptor, also binds

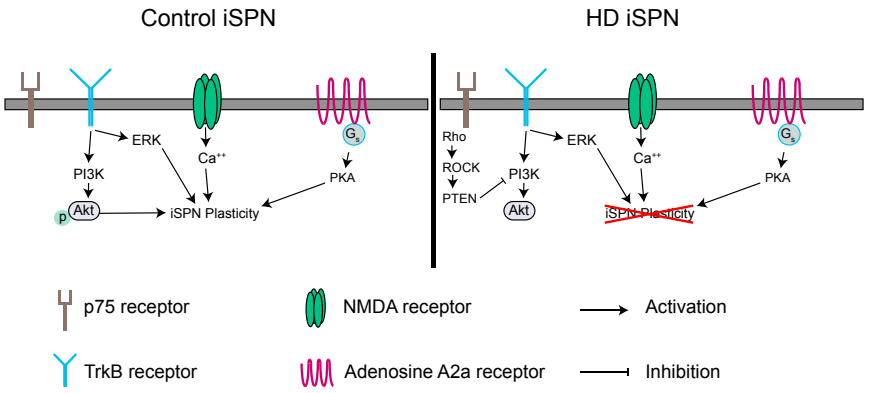

Figure 1. Mechanisms of iSPN Plasticity and Its Impairment in Huntington's Disease
Diagram depicting the signaling pathways required to induce potentiation at corticostriatal synapses in iSPN (left) and the aberrant signaling observed in the BACHD mouse (right).

BDNF albeit with a lower affinity (Figure 1). Specifically, the expression of phosphatase and tensin homolog (PTEN) downstream of p75 receptor activation is enhanced exclusively in HD iSPNs. Knockdown or inhibition of p75 or its downstream targets restores plasticity in these cells.

Aside from its relevance to HD, this study comprehensively describes a novel form of synaptic potentiation in the striatum. By examining potentitation at the level of individual neurons, Plotkin et al. (2014) have revealed strict induction criteria that are required to observe potentiation at glutamatergic synapses in the striatum. First, potentiation is dependent on convergent signaling between TrkB, NMDA, and G protein-coupled receptors; antagonism of any one component is sufficient to inhibit plasticity. Second, potentiation is restricted to only corticostriatal synapses and does not appear to occur at thalamostriatal synapses. Third, iSPNs and dSPNs differ in the G protein-coupled receptor that is involved in plasticity induction. By describing this form of plasticity in-depth, Plotkin et al. (2014) have provided the community with a valuable tool to assess potentiation at defined synapses onto phenotypically identified striatal neurons that will be useful for assessment of corticostriatal plasticity in other movement disorders.

While unable to replicate the previous general understanding of a BDNF deficit in HD, Plotkin et al. (2014) clearly show a plasticity deficit in the HD striatum that is specific to iSPNs and is a result of altered signaling downstream of a BDNF receptor. These data provide valuable clues toward developing better treatment for involuntary movements in early symptomatic HD. Given the known deleterious signaling mediated by the p75 receptor (reviewed in Fujii and Kunugi, 2009), targeting this pathway may also offer neuroprotection. On the other hand, the previous literature highlighting a BDNF production and delivery deficit is simply too large to ignore. Taking all findings into account, there remains some uncertainty as to how to proceed with therapeutic development in HD. For example, if BDNF production and delivery deficits significantly contribute to HD pathogenesis as previously thought, then perhaps the concentration of BDNF released in the HD striatum by synaptic activity would be too low to significantly coactivate the relatively low-affinity p75 receptor. It should be noted that the BACHD model shows reduced synaptic activity at the age at which the plasticity deficit is observed (Gray et al., 2008). Thus, it remains unclear whether agonizing TrkB receptors, antagonizing p75 receptors, or a combination of both would produce the most favorable effect. Indeed, it was recently shown that long-term systemic treatment with LM22A-4, a specific TrkB agonist without actions at the p75 receptor, ameliorated the spine loss and motor symptoms in HD mice (Simmons et al., 2013). It is possible that simultaneous inhibition of the p75 receptor could augment these beneficial effects. In any case, the results of Plotkin et al. (2014) caution strategies aiming to simply increase general BDNF levels and provide convincing evidence to support p75 antagonism in the treatment of early symptomatic HD.

As with all good studies, many questions are answered while others are raised. Since the form of corticostriatal synaptic plasticity described here is novel, its relevance to movement regulation, and therefore its importance to HD pathology, remains unknown. It would be of great interest to determine whether inhibitors of the p75 receptor or its downstream signaling—treatments that restore iSPN plasticity—can rescue motor deficits observed in the BACHD model (Gray et al., 2008). The results reported here also raise questions as to the mechanism(s) underlying the mutant huntingtin-associated increase in PTEN expression and function. Moreover, the question of why the BDNF/TrkBR signaling network in the BACHD mice is attenuated selectively in striatal iSPNs while it is elevated in dSPNs remains to be addressed. On a separate note, accumulating evidence suggests that NMDA receptors located outside of the synapse (extrasynaptic NMDARs) can impair synaptic potentiation in the hippocampus (reviewed in Parsons and Raymond, 2014); although extrasynaptic NMDAR activation is known to be enhanced in HD striatal neurons (Milnerwood et al., 2010), the striatal synaptic potentiation here was restored after p75 signaling inhibition. The role of extrasynaptic NMDARs, if any, in this form of corticostriatal plasticity remains to be determined.

The exciting findings presented in Plotkin et al. (2014) are sure to spark interest, and perhaps some controversy, as to the precise role of BDNF in HD pathogenesis. Further investigation of a variety of HD mouse models as well as human brain tissue at different HD stages, to determine the contribution of a BDNF production and delivery deficit (or lack thereof), is crucial for guiding therapeutic strategies. Nonetheless, the newly described form of striatal plasticity should prove valuable for future studies into the mechanisms underlying a variety of movement disorders. Last, but certainly not least, the highlighted contribution of the p75 neurotrophin receptor and its downstream

signaling in HD striatum parallels studies that demonstrate a role for this receptor in other neuropsychiatric disorders (Fujii and Kunugi, 2009) and provides a novel, promising set of therapeutic targets for the treatment of HD.

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Learning by Example in the Hippocampus

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Learning can be facilitated by previous knowledge when it is organized into relational representations forming schemas. In this issue of *Neuron*, McKenzie et al. (2014) demonstrate that the hippocampus rapidly forms interrelated, hierarchical memory representations to support schema-based learning.

One of the timely questions of hippocampal research is to understand how learning influences hippocampal neuronal representations. New information may be incorporated into already existing representations or entirely new representations could be formed to prevent interference with previously formed memories. Schema-based learning would require the formation of interrelated memory representation into which new information could be rapidly assimilated (Tse et al., 2011). In this issue of *Neuron*, McKenzie et al. (2014) show that hippocampal cognitive maps can form such representations: different representations can be hierarchically organized, incorporating both spatial and task-related mnemonic information.

Using two different environments linked by a tunnel (Figure 1A), McKenzie et al. (2014) probed how hippocampal firing patterns reflect learned associations between objects, the presence of a reward, and environment (or context). Rats had to learn that in the first environment, one of two objects (flower pots, scented with different odors and containing different digging media) was rewarded, even when the position of the objects was swapped around. In the second environment, the rules were reversed, so that the other object was rewarded. Once learned, animals were able to associate the presence of a reward with new objects over far fewer trials, consistent with a schema-based learning. How does the hippocampal network encode different features of this task? And how is new information incorporated into previously formed representations?

To answer these questions, McKenzie et al. (2014) recorded from CA3 and CA1 pyramidal cells as rats performed this task, with two sets of objects (AB or CD), in randomly interleaved trials, focusing on the firing patterns around the point at which the animal sampled the object (Figure 1A). The majority of recorded cells showed differential firing responses, depending on the location or identity of the object sampled. In addition to position, many cells also encoded information about the object, including the object's identity, the set (AB or CD) to which it belonged, and whether the object was baited or not (valence). In this way, hippocampal population activity, or "cell assemblies" of such neurones, can collectively represent the spatial and nonspatial features of the task.

If cell-assembly coding of memory traces reflect distinct and separate representations, one might expect the